Principles of Clinical Pharmacology,
NIH, April 24, 2000

Role of FDA in Guiding Drug Development

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Why **FDA ?**

When **does FDA get involved ?**

How **does FDA guide drug development?**

What **comprises FDA guidance ?**

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Guiding Drug Development
Why FDA?

- FD&C Act: history and its supporters
  - a uniquely American phenomenon
  - resulted from public safety disasters
    - ~ 1900, 1938, 1960, 1972, 1987
- Evolution of Drug Regulation (R. Temple)

SAFETY → EFFECTIVENESS → INDIVIDUALIZATION
….. → PERSONALIZATION

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When does FDA get involved ?

- Preclinical (voluntary) phase
  - animal testing
  - subpart E, Fast Track
- Clinical development phase
  - IND
- Marketing phase
  - ADR surveillance
  - new uses, product changes

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How does FDA guide drug development?

- Written guidances
  - Regulations, guidelines (incl. ICH), guidances[1]
  - Regulatory letters
  - (Statute, Congressional Reports)
- Face-to-face meetings
- FDA Advisory Committee meetings
- Podium presentations

1 Website - www.fda.gov CDDS 2000

What comprises FDA guidance ?

- Standards
  - chemistry and manufacturing controls (CMC)
  - preclinical animal toxicology requirements
  - ethics of human clinical trials
  - documentary requirements for INDs, & NDAs
- Clinical trials
  - safety
  - effectiveness
  - trial design

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FDA *Today*: Increasing Transparency

- **GUIDANCES** (http://www.fda.gov/cder/guidance.htm)
  - *344* guidances (final/draft, FDA/ICH), 31-MAR-00

- **Guidance documents:**
  - *Cannot legally bind FDA or the public*
  - *Recognition of the value of consistency & predictability*
  - *Because a company wants assurance*
  - *So staff will apply statute & regulations consistently*

--"The FDA's Development, Issuance, and Use of Guidance Documents," Fed Reg: Feb. 27, 1997

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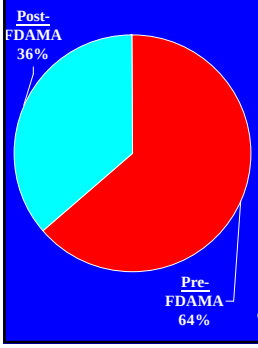
FDA *Today*: Increasing Transparency



Pre-FDAMA
- 228 guidances
- 243 month period
- **= 11.1 guidances/year**

Post-FDAMA
- 130 guidances
- 28 month period
- ★ **= 55.7 guidances/year** ★

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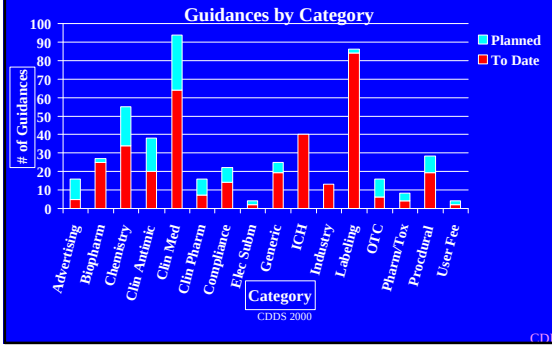
FDA *Tomorrow*: Planned Guidances



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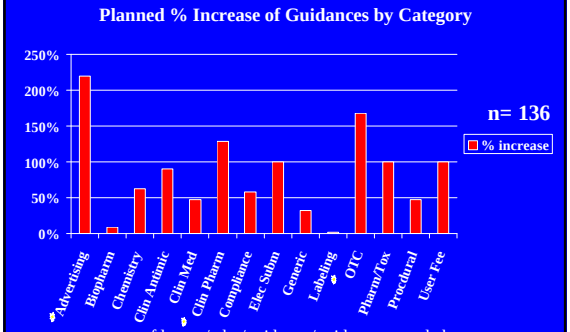
FDA *Tomorrow*: Guidance Topics



www.fda.gov/cder/guidance/guidance-agenda.htm

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EXAMPLE 1
Clinical/Pharmacological Guidances*

1. **Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies *In Vitro*** (97); ***In Vivo*** (99)
2. **Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application** (98)
3. **Pharmacokinetics in Patients with Impaired Renal Function** (98)
4. **Population Pharmacokinetics** (99)

* Website - www.fda.gov

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EXAMPLE 2
Clinical/Pharmacological (*Draft*) Guidances*

1. **General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products** (11/98)
2. **Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling** (11/99)

* Website - www.fda.gov

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EXAMPLE 3
Clinical/Medical Guidances[1]

- ***Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*** (98)
- **Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs** (93)
- **Study of Drugs ... used in the Elderly** (89)
- **Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research (draft 3/00)**

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* 41 final, 12 draft guidances Website - www.fda.gov

New Formulations and Doses of Already Approved Drugs*

- Where ***blood levels ... are not very different***, it may be possible to conclude ... is effective on the basis of **pharmacokinetic data *alone***.
- Even ***if blood levels are quite different***, if there is **a well-understood relationship between blood concentration and response**, ..., it may be possible to conclude ... is effective on the basis of **pharmacokinetic data *without*** an additional clinical efficacy trial.

* **Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products", May 1998**

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EXAMPLE 4
Biopharmaceutics Guidances*

- **Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design** (92)
- **Trazodone Hydrochloride (tablets) In Vivo Bioequivalence and In Vitro Dissolution Testing** (88)

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* Website - www.fda.gov

EXAMPLE 5
FDA Modernization Act of 1997 "FDAMA"

- Sec. 111. ***Pediatric*** studies of drugs
  - **PK bridging studies**
- Sec. 115. Clinical investigations
  - **support of *one* adequate and well-controlled clinical investigation by *"confirmatory evidence"* comprising PK or PK/PD**

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FDAMA, Sec. 111
Pediatric studies of drugs

"(g) Definitions. - the term `pediatric studies' or `studies' means at least one clinical investigation (that .. may include *pharmacokinetic* studies) in pediatric age groups...."

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Pediatric Labeling Regulations
(21 CFR 201.56)

"FDA may approve a drug for pediatric use based on ... studies in adults, with other information supporting pediatric use…. additional information supporting pediatric use must ordinarily include data on the *pharmacokinetics* of the drug in the pediatric population ….Other information, such as data on ***pharmacodynamic*** **studies**….."

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FDAMA, Sec. 115

Clinical investigations

"If the Secretary determines, based on relevant science, that data from *one* adequate and well-controlled clinical investigation and *confirmatory evidence* …. are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence.."

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FDAMA, Sec. 115
Clinical investigations

CONGRESSIONAL COMMITTEE REPORTS[1]

- *"confirmatory evidence"* = "scientifically sound data from any investigation in the NDA that provides substantiation as to the safety and effectiveness of the new drug"
- confirmatory evidence = "consisting of earlier clinical trials, *pharmacokinetic* data, or other appropriate scientific studies"

1 House Commerce Committee, 10/7/97, and Committee of Conference on Disagreeing votes of the two Houses, 11/9/97

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SOME OBSERVATIONS

- **FDA clinical guidances are increasingly based on *principles of clinical pharmacology***
- **"guidance" versus "regulation"**
  - **value added versus barrier**
- **FDA guidance**
  - **national "treasure" versus "national nuisance"**
  - **a bargain !**
- **Value of FDA guidance is related to the quality of sponsor data and preparation**

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